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Neuro-HIV—New insights into pathogenesis and emerging therapeutic targets

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Abstract

HIV-associated neurocognitive disorders (HAND) is a term describing a complex set of cognitive impairments accompanying HIV infection. Successful antiretroviral therapy (ART) reduces the most severe forms of HAND, but milder forms affect over 50% of people living with HIV (PLWH). Pathogenesis of HAND in the ART era remains unknown. A variety of pathogenic factors, such as persistent HIV replication in the brain reservoir, HIV proteins released from infected brain cells, HIV-induced neuroinflammation, and some components of ART, have been implicated in driving HAND pathogenesis in ART-treated individuals. Here, we propose another factor—impairment of cholesterol homeostasis and lipid rafts by HIV-1 protein Nef—as a possible contributor to HAND pathogenesis. These effects of Nef on cholesterol may also underlie the effects of other pathogenic factors that constitute the multifactorial nature of HAND pathogenesis. The proposed Nef- and cholesterol-focused mechanism may provide a long-sought unified explanation of HAND pathogenesis that takes into account all contributing factors. Evidence for the impairment by Nef of cellular cholesterol balance, potential effects of this impairment on brain cells, and opportunities to therapeutically target this element of HAND pathogenesis are discussed.

Keywords

cholesterol; epigenetic modifications; extracellular vesicles; HAND; HIV; inflammation; lipid rafts; Nef; trained immunity

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AUTHOR CONTRIBUTIONS

Both authors were involved in generating the idea and drafting the manuscript.

DISCLOSURES

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1 | INTRODUCTION

HIV-associated neurocognitive disorders (HAND) are one of the most abundant comorbidities of HIV infection, affecting about 50% of HIV-infected individuals.[1] HAND prevalence in people living with HIV (PLWH) is up to five-fold higher than the prevalence of neurocognitive impairment in general population.[2-4] Clinically, HAND is characterized by a progressive cognitive decline reflected initially by neuronal dendritic simplification and mild cognitive disorders, but, ultimately, with neuronal loss and advent of dementia. At the neuropathological level, the gray matter may display focal damage, and there are abnormalities in the white matter.[4]

In the brain, HIV resides primarily in resident microglial cells, and also in some astrocytes, as well as in monocytes/macrophages migrating from the blood, while most evidence suggests that neurons are not infected by HIV.[5-7] Therefore, HIV-associated neuronal damage must be predominantly an indirect effect of HIV infection. With the advent of combination antiretroviral therapy (ART), prevalence of the severe form of HAND, HIV-associated dementia (HAD), has diminished, but that of milder forms, minor neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI), have increased,[8] suggesting that ART slowed, but did not stop the progression of the disease. The mechanism of how few infected cells may cause such a persistent effect on the brain is not well understood.

2 | CHOLESTEROL METABOLISM, LIPID RAFTS, AND NEUROCOGNITIVE DISORDERS

Brain is the most cholesterol-rich organ in the body, containing about 20% of whole cholesterol content.[9] Most of this cholesterol constitutes the myelin sheaths, which insulate axons and facilitate neuronal communications. As an essential component of neuronal membranes, cholesterol is involved in the formation of synapses and dendrites.[10,11] It is not thus surprising that cholesterol homeostasis in the brain is tightly regulated and an impairment of cholesterol metabolism and transport leads to functional defects.[12] Majority of neurocognitive disorders are bona fide neurodegenerative diseases, and involvement of cholesterol metabolism in the pathogenesis of neurodegeneration is well established: Alzheimer's disease, Parkinson's disease, and prion diseases all have established connections with cholesterol metabolism.[13] Genetic mutations in genes controlling cholesterol biosynthesis or metabolism are associated with severe neurological diseases, such as Niemann-Pick type C disease, desmosterolosis, and Smith–Lemli–Opitz syndrome (reviewed in Ref. [14]). Inactivation of cholesterol transporter ABCA1 in the mouse brain was shown to affect synaptic transmission and mouse behavior.[15] Also, a correlation between Alzheimer's disease and impairment of ABCA1-mediated cholesterol efflux has been established.[16,17] APOE4, the strongest genetic correlate of Alzheimer's disease, was shown to affect cholesterol homeostasis in the brain and reduce myelination.[18]

Impairment of cholesterol homeostasis is tightly linked to functional and structural impairment of the lipid rafts, the specialized cholesterol-rich microdomains of the plasma membrane.[19] Lipid rafts are essential for many neuronal functions, including signal

transduction initiated by several classes of neurotrophic factors, neuronal cell adhesion, axon guidance, and synaptic transmission,[20] and agents affecting the lipid rafts cause neuronal dysfunction.[21,22] While impairment of cholesterol homeostasis in various nonneuronal cell types can contribute to neurodegeneration, it is neuronal dysfunction and neuronal death that are the essence of this pathology. There is overwhelming evidence that a primary cause of neuronal dysfunction in many neurodegenerative diseases is misfolding and subsequent oligomerization/aggregation of an amyloidogenic protein.[23] Many, if not most, neurodegenerative diseases have a “prion-like” feature in their pathogenesis, where a misfolded protein causes misfolding of other copies of itself[24] or of a different protein.[25] Two conditions are required for the misfolding process to spread around the brain and to progress into a disease: (i) initial presence of a misfolded copy of an amyloidogenic protein (which is a result of a mutation, an infection, a trauma, hypoxia, or is a spontaneous event), and (ii) high local concentration of the normal copies of the protein to allow nucleation and propagation to occur at a rate overwhelming protective mechanisms.[24,26] A common feature of neurodegenerative diseases is the accumulation of amyloidogenic proteins in lipid rafts.[27] Concentration of amyloidogenic proteins in rafts makes these proteins susceptible to aggregation. It is plausible that the abundance of rafts, and consequently the availability of sites where proteins are present at high local concentration, is a key prerequisite for a neurodegenerative disease to progress. Furthermore, rafts are also home to inflammatory receptors, such as TLR4, that initiate inflammatory signaling cascades,[28] they also house apoptosis receptors, such as TNFR1, that trigger apoptotic signaling.[29,30] Finally, rafts house many neurotransmitter receptors and are critical for the release of neurotransmitters.[31] Overall, there is solid support in the literature that aberration of cholesterol homeostasis in the neurons, via impairment of the structure and function of the lipid rafts, may be a causative factor in the development of neurocognitive impairment.

3 | CHOLESTEROL METABOLISM AND HIV LIFECYCLE

Cholesterol metabolism and lipid rafts also play a key role in the lifecycle of HIV, as major steps of viral replication, such as entry and viral release, occur through the lipid rafts.[32] Thus, since overabundance of lipid rafts favors HIV replication, it is not surprising that the virus has evolved mechanisms to manipulate the abundance of lipid rafts by closely interacting with host cholesterol homeostasis machinery.[33] HIV proteins Tat and Nef have been shown to stimulate the expression of cholesterol biosynthesis genes.[34-36] Nef also impairs the reverse cholesterol transport pathway, which is responsible for the removal of excessive cholesterol from peripheral cells, by inducing degradation of the key element of this pathway, the lipid transporter ATP-binding cassette subfamily A member 1 (ABCA1).[37] Furthermore, since ABCA1 activates small GTPase Cdc42, which regulates polymerization of actin,[38-40] inhibition of ABCA1 activity by Nef reduces F-actin polymerization inducing changes in the cytoskeleton, a second mechanism increasing the abundance of lipid rafts.[41] Together, these effects lead to the accumulation of intracellular cholesterol[37,42] and, importantly, increased abundance of the lipid rafts[43] (Figure 1). Notably, ability to affect ABCA1 is common to Nef from all tested HIV and SIV isolates, although some variations in the magnitude of this activity between different viral isolates were detected.[37] Given that Nef appears to be the most potent HIV-derived factor to affect lipid rafts, as it influences

both cellular synthesis and efflux of cholesterol as well as perturbations of cytoskeleton, we focus on this protein.

Nef was initially described as a “Negative factor” that downregulates HIV-1 transcription and promotes latency.[44,45] Later studies demonstrated that Nef is the major pathogenic factor of HIV-1, and pathogenicity of Nefdeficient viral mutants is greatly attenuated.[46,47] Despite its small size (27–32 kDa), Nef is involved in many protein–protein interactions, affecting expression of multiple cellular proteins (e.g., CD4, MHC-I, SERINC5) to suppress antiviral immune responses, promote infectivity, and optimize viral replication (for reviews, see Refs. [48-50]). Expression of Nef alone in transgenic mice induces the development of disorders that reproduce many features of AIDS[51] and human comorbidities associated with HIV infection, including cardiac disease,[52] B-cell dysfunction,[53] and nephropathy[54] (reviewed in Ref. [55]).

In addition to expression within infected cells, Nef is also released into the extracellular environment in extracellular vesicles (EVs).[56,57] Extracellular vesicles secreted by HIV-infected cells and containing Nef, as well as other HIV or host proteins and miRNAs, were previously implicated in having direct or indirect toxic effects on neurons.[58] Nef EVs circulate in the blood and can be detected even in HIV-infected patients successfully treated with ART and having an undetectable HIV load for several years.[56,57,59] Circulating Nef EVs were shown to affect cholesterol homeostasis of bystander cells similar to internally produced Nef: they diminish ABCA1 abundance, inhibit cholesterol efflux, and increase cellular cholesterol content and lipid raft abundance.[41,60] Changes in lipid rafts promote hyperreactivity of myeloid cells to inflammatory stimuli, which may underlie persistent inflammation in HIV-infected individuals.[41,61] EVs may be particularly effective in delivering Nef to cells around the body as these vesicles are known to either directly translocate the cargo into the cell cytoplasm or create effective high local concentrations of cargo molecules in the vicinity of cells.[62] EVs may also protect carried Nef from the activity of proteases and neutralizing antibodies[63] and they can pass through the blood–brain barrier (BBB).[64,65] Nef was found in the brains of PLWH[66-68] and of SIV-infected macaques,[69] where it could have been delivered from periphery as well as produced by infected brain cells.[67] Due to its ability to modify lipid rafts, which may underlie such pathogenic activities of Nef as inflammation, impairment of intra- and intercellular signaling, impairment of autophagy, and induction of apoptosis, Nef may play a substantial role in pathogenesis of HAND.[70]

4 | PATHOGENESIS OF HAND

4.1 | Complexity of HAND pathogenesis

HAND is a complex disease with multiple factors contributing to its pathogenesis, progression, and outcomes (Figure 2 and Ref. [2]). These factors can be divided into four main groups: HIV-related factors (HIV proteins Tat, Nef, and gp120, ART, length of infection, level of immunodeficiency); coinfections and other comorbidities that influence pathogenesis of HAND; behavioral, social, and environmental factors; and nonmodifiable factors (age, sex, ethnicity, genetic background). All these factors have a considerable influence on the course of the disease (Figure 2), but most of them are not strictly essential

for its development. By definition, HIV infection is essential for HAND, whereas any of the other factors may be absent in an affected individual developing HAND. Almost 50% of HIV-infected individuals suffer from some form of HAND,[1] and it remains possible that a proportion of the other 50% may have it in an early asymptomatic and undiagnosed stage. Although HAND in aging population may have similarities with clinical characteristics and pathological features of cognitive diseases in uninfected individuals, HAND in younger population has very specific features discriminating it from other neurocognitive diseases.[71,72] It appears plausible that HAND is a distinct neurological disease, with non-HIV factors defining the specifics of individual disease variations grouped under this general term.

Among the HIV-related factors, Nef has a unique role in HAND pathogenesis due to a combination of pathogenic activities it can exert.[70] First, Nef appears to be the only, or at least the major, HIV protein that is constantly produced and secreted into the blood even in individuals controlling HIV replication by ART or in elite controllers naturally controlling HIV infection.[59,73] Second, Nef is involved in pathogenic processes that are directly linked to neuropathology, such as neuroinflammation,[74,75] modulation of autophagy,[76,77] and apoptosis.[69,78] These activities may or may not be linked to Nef's impact on cholesterol metabolism and lipid rafts (see below). Nef is one of the most variable HIV proteins, and the question of neuropathogenicity of different Nef variants has high clinical relevance. Computational analyses did not detect unique features specific to Nef from brain isolates of HIV-1 but identified certain structural features that may determine the neuropathogenicity of Nef.[67]

We propose that the Nef-cholesterol-lipid raft axis may underlie the neuropathogenic effects of Nef (see below). Nef may contribute to HAND directly (e.g., by inducing a cascade of protein misfolding), but also indirectly, by potentiating or even triggering the effects assigned to several other contributing factors. An example of such indirect effect is Nef-induced changes in the lipid rafts promoting neuroinflammation characteristics for neurocognitive diseases (see below). Although Nef may not be responsible for all physiological and psychosocial comorbidities that disproportionally impact PLWH,[79,80] the proposed hypothesis provides explanation and mechanisms for the key features of HAND.

4.2 | Neuroinflammation

Chronic neuroinflammation is widely accepted as a major contributor to HAND as well as other neurodegenerative diseases.[81] In the ART era, the majority of virologically suppressed HAND patients do not display pathological evidence of severe encephalitis,[82] and under physiological conditions, low-level inflammation in the brain is usually asymptomatic.[83] Nevertheless, elements of inflammation in the brain, such as accumulation of mononuclear phagocytes, related microglial activation and astrocytosis, and decreased synaptic and dendritic density, are observed in postmortem samples from HIV patients.[84] Inflammatory responses in the brain can damage neurons via neurotoxins released by activated microglia[85,86] as well as cause the release by glial and microglial cells of reactive oxygen species and nitric oxide, which can induce apoptosis of neurons and other brain resident cells.[87]

While it is clear that neuroinflammation contributes to pathogenesis of HAND, why it persists in ART-treated HIV-infected individuals with undetectable viral load remains unresolved. A common explanation invokes the generalized low-grade inflammation that accompanies HIV disease and is related to incomplete recovery after ART initiation of intestinal lymphoid tissue and the disruption of the barrier that it creates to microbial product leakage into the blood circulation.[88,89] This explanation was questioned in a recent report that did not find association between increased gut epithelial permeability and HIV-associated immune activation in a small cohort of well-controlled HIV-positive patients on antiretroviral therapy.[90] On the other hand, the role of cholesterol metabolism and lipid rafts in inflammation is well documented.[91] In addition to housing inflammatory and apoptotic receptors, expansion of the lipid rafts in bone marrow hematopoietic stem cells increases the expression levels and signaling of growth factor receptors, causing the proliferation of myeloid cells that also promotes inflammation.[92,93] Furthermore, cholesterol crystals that form in cholesterol-rich cells activate the NLRP3 inflammasome.[94] As mentioned above, most of these effects were observed in myeloid cells treated with Nef EVs. Moreover, Nef EVs promoted inflammatory responses of microglial cells[95] and astrocytes,[75] suggesting that brain myeloid cells are not exempt from proinflammatory activity of Nef EVs. Nef EVs can be released by HIV-infected cells in the brain, including astrocytes[96] and microglia,[95,97] or can originate from blood as most EVs can cross BBB.[58] Thus, elevation of lipid rafts followed by potentiation of neuroinflammation in patients with HIV disease may be one element of contribution of Nef EVs to the pathogenesis of HAND.

4.3 | Neurotoxicity of HIV proteins and ART

Another suggested contributor to HAND pathogenesis is the neurotoxic effect of several HIV proteins and/or components of the ART cocktails. Indeed, apoptosis of neurons is a key feature of the late stages of neurodegeneration.[23] In HAND, apoptosis of neurons was proposed to be associated with Nef, Env, and Tat, which have been shown to cause neuronal apoptosis in vitro.[84] Nef EVs at high concentrations were shown to be cytotoxic to neurons and glial cells[97] as well as to brain microvascular endothelial cells.[98] Cholesterol metabolism was not investigated in these studies, so it is unclear whether the observed effects were related to the impairment of cholesterol homeostasis and dysregulation of lipid rafts, but apoptosis, like inflammation, may also be secondary to the impairment of cholesterol homeostasis and specifically the impairment of ABCA1 and lipid rafts.[99] Furthermore, it remains uncertain whether concentrations of HIV proteins in the brain reach levels high enough to cause neurotoxicity directly, especially when HIV replication is suppressed by ART. Finally, apoptosis and cell death are not prominent in ANI and MND, which are the predominant forms of HAND in the ART era.

ART components may be neurotoxic, especially given the life-long course of anti-HIV treatment.[100] Nucleoside reverse transcriptase inhibitors (NRTI), the most common component of modern ART cocktails, affect mitochondrial polymerase γ and cause mitochondrial toxicity, which may impair functions of astrocytes and neurons.[101,102] However, no direct clinical association between NRTI use and HAND has been found. Another popular component of ART is integrase inhibitors, which are not associated with significant neurocognitive impairment except mild neuropsychiatric effects.[103] Significant

neurotoxicity has been reported for nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz[104] as well as for several drugs from the protease inhibitor class.[100] Currently, these drugs are not the preferred components of the ART cocktails. Overall, although certain anti-HIV drugs can cause neurotoxicity, modern compositions of ART are mostly free of adverse neurological effects and are unlikely to contribute to HAND.

4.4 | HAND and Alzheimer's disease

An interesting hypothesis suggests that HAND may be an accelerated form of Alzheimer's disease (AD).[105] Indeed, HAND has many similarities with AD, such as neuroinflammation, similar transcriptional signatures, and increased abundance and changed localization of intracellular beta amyloid (Aβ), a critical component in AD pathogenesis.[106-109] However, there are several important differences between these diseases. For example, AD-specific pathology was less prevalent and less severe in HIV-infected persons as compared to those without HIV.[110] Soluble amyloids either remain unaltered or are increased in AD, while in HAND patients, they are decreased.[105] Also, the cognitive trajectory associated with abnormal p-tau accumulation in HAND was unlike the rapid deterioration seen in AD.[111] While the possibility that HIV infection accelerates the underlying AD is an attractive hypothesis, accumulating evidence suggests that HAND and AD are distinct pathologies,[72] and it may be more appropriate to describe the similarities between these diseases by the term “Alzheimer's-like pathology” when HAND is concerned.[105] On the other hand, impairment of cholesterol homeostasis and modification of lipid rafts, which is characteristic of Alzheimer's disease,[112,113] as well as the reliance of both AD and HAND on the transport of proteins by EVs[114] may connect pathogenesis of both diseases and provide the missing link for explaining their similarities.

5 | A UNIFIED HYPOTHESIS OF HAND PATHOGENESIS

As described in several reviews[115,116] and mentioned above, the key element of pathogenesis of neurodegeneration is misfolding amyloidogenic proteins, triggered and/or accelerated by chronic neuroinflammation, toxic environment, or genetic background. HIV disease provides both a favorable milieu for neurodegeneration to occur and rapidly progress and a trigger to turn it on. The key contributor to these effects may be Nef. In our hypothesis, aimed at describing the mechanisms of neurodegeneration specifically associated with HIV infection, we propose the following sequence of events: (i) HIV-infected cells in viral reservoirs, both in the brain (microglia, astrocytes and perivascular macrophages)[117] and periphery, secrete Nef EVs into systemic circulation and into CSF;[97,118] Nef EVs are taken up by neurons causing a reduction of cellular ABCA1 and leading to the increased abundance and modification of lipid rafts (Figure 1); (ii) accumulation of amyloidogenic proteins in modified lipid rafts leads to their misfolding and aggregation (Figure 3); (iii) increased abundance and modification of lipid rafts in neurons exacerbates inflammatory signaling originating from inflammatory receptors in the rafts (e.g., TNFR, TLR4) (Figure 3), as well as impairs the function of ionotropic neurotransmitter receptors (e.g., NMDA); and (iv) amyloidogenic protein misfolding, increased inflammatory signaling and impaired neurotransmission lead to neuronal dysfunction and ultimately to neuronal death. It is important to recognize that glial,

microglial, and endothelial cells are also involved in the pathogenesis of CNS dysfunction and are also affected by Nef.

We have recently demonstrated[60] that treatment of neuronal cells, SH-SY5Y, with Nef EVs reduces ABCA1 and cholesterol efflux leading to the increased abundance of lipid rafts and inflammatory signaling. Moreover, treatment of SH-SY5Y cells with Nef EVs increased the abundance of two lipid raft-associated proteins that play a key role in the pathogenesis of AD, amyloid precursor protein (APP), and Tau.[60] Treatment of neuronal cells with Nef EVs had functional consequences: sensitivity of neurons to glutamate-induced excitotoxicity was sharply elevated, as was acetylcholinesterase activity. Our analysis of NNTC-provided postmortem brain samples from HIV-infected individuals receiving ART[68] detected Nef in 12 out of 22 HAND samples. When we compared brain samples with and without Nef, the former had less ABCA1, more lipid rafts, more p-Tau, and higher HAND clinical score. Further, we found a positive correlation between p-Tau and flotillin-1 (raft marker) and Nef. These findings are consistent with the key initial steps of the proposed hypothesis: impairment of ABCA1 by exNef induces formation of aberrant lipid rafts in neuronal cells leading to accumulation of amyloidogenic proteins in the rafts and neuronal dysfunction.

6 | TRAINED INNATE IMMUNITY—A POSSIBLE CONTRIBUTOR TO HAND

Another recently discovered mechanism by which Nef EVs may promote inflammation is trained innate immunity (TRIM).[79] TRIM is a relatively new idea that innate immune cells can acquire memory from an infectious agent. This memory regulates innate immune response to subsequent infection, even with an agent different from the one that induced memory. In contrast to classical immune memory of T and B cells, which is regulated at the genetic level, innate memory is achieved by epigenetic and metabolic reprogramming that can be induced by a variety of agents, including bacterial, fungal, and viral components, cytokines and TLR agonists, via stimulation of pattern recognition receptors.[119-127] Recent findings from our group demonstrated that Nef EVs can induce immune training in monocytes and myeloid progenitor cells by a mechanism dependent on stimulation of glycolysis and changes in cholesterol homeostasis and lipid rafts,[128] resembling the mechanism described for β-glucan[129] (Figure 3). Similarity between the trained immunity mechanisms induced by β-glucan and Nef EVs is supported by their sensitivity to inhibitors of cholesterol biosynthesis and IGF1R signaling, stimulation of glycolysis, and activation of pro-inflammatory genes via epigenetic modifications.[128,129] Intermediates of glycolysis, fumarate, and acetylcoenzyme A (Ac-CoA) inhibit KDM5 histone demethylase and stimulate histone acetyl-transferase, respectively, modifying the H3 histone to a transcriptionally active conformation,[129] which underlies overresponsiveness of Nef-treated cells to inflammatory stimuli.[128] Ac-CoA also stimulates cholesterol biosynthesis, a side product of which, mevalonate, is secreted and interacts with IGF1R, initiating a signaling cascade that further stimulates glycolysis and cholesterol synthesis, enhancing epigenetic modifications and expansion of lipid rafts, where IGF1R is localized (Figure 3). Interestingly, epigenetic changes appear to suppress the expression of ABCA1 in Nef EVs-treated cells, the effect that was not described for β-glucan and which may further enhance ABCA1 inhibition induced by Nef EVs.[128] This concept is yet to be tested in brain cells, but if confirmed, this finding opens a possibility that chronic neuroinflammation

may be maintained in HIV-infected individuals even when all HIV-specific factors are eliminated.[130]

7 | NOVEL APPROACHES FOR THE TREATMENT OF HAND

7.1 | Targeting cholesterol metabolism

Pharmacological targeting of cholesterol metabolism is an established therapeutic approach due to the critical role of cholesterol in pathogenesis of atherosclerosis, the main cause of coronary heart disease. Based on the arguments presented above, impairment of cholesterol homeostasis is also a plausible player in HAND pathogenesis. If this mechanism is proven, one can envision new treatments that may stop or reverse the development of HAND. Some cholesterol-lowering drugs, successfully used for a long time in the context of cardiovascular diseases, such as statins, show some activity in mitigating neurodegeneration[131,132] and may be especially beneficial in the treatment of HAND. This opens a way to test other modern approaches to lowering cholesterol, such as PCSK9 inhibitors and ASO, so long as they are able to penetrate BBB.

Some new cholesterol-targeting drugs are already in pre-clinical or clinical trials for the treatment of brain diseases. For example, cyclodextrin has been shown to stop the progress of Niemann-Pick type C disease in mouse models.[133,134] This drug extracts cholesterol from cellular membranes and may reduce neuroinflammation in HAND, possibly, by targeting lipid rafts. This anti-inflammatory activity may be the reason for its neuroprotective activity in cellular and mouse models of Alzheimer's disease.[135] The similar, but more physiologic mechanism is behind neuroprotective action of apolipoprotein A-I mimetic peptides.[136] Another approach to counteract HAND neuropathy is to stimulate ABCA1 expression, which is suppressed by Nef. Among the most potent stimulators of ABCA1 expression are agonists of liver X receptor (LXR).[137] A synthetic LXR agonist T0-901317 was shown to reduce neuropathological changes and improve memory in mouse models of experimental dementia.[138,139] Another LXR agonist, GW3965, reduced the accumulation of β-amyloid and improved synaptic function in mice.[140] These drugs may be even more potent in the context of HAND given the key role of ABCA1 suppression in Nef-induced neuropathology.

7.2 | Lipid raft therapy

Given the prominent role of lipid raft impairment in pathogenesis of HAND, targeting specifically lipid rafts appears to be an attractive option. We have recently described various forms of lipid raft therapy.[141] Some of the approaches of lipid raft therapy overlap with those affecting cholesterol homeostasis, such as LXR agonists and cyclodextrins, others employ a different principle. Two of the latter approaches stand out. One is apolipoprotein A-I Binding Protein (AIBP),[142] an innate factor that appears to selectively target lipid rafts on activated cells, normalizing their abundance and function impaired by inflammatory stimuli.[143] Neuroprotective effects of AIBP have been shown in a murine model of neuropathic pain.[143,144] Another is the overexpression of caveolin-1, an approach unique because it targets the composition and “quality” of rafts, rather than their abundance.[145]

7.3 | Nef EVs and treatment of HAND

Provided the key role of Nef EVs in HAND pathogenesis is proven, the most direct approach to treat this comorbidity would be to neutralize the Nef EVs or prevent their interaction with the cells. This goal appears feasible given the published description of Nef-binding protein on the cell surface,[146] which may serve as a binding site for Nef-carrying EVs, and our recent finding that Nef localizes on the outer membrane of EVs (manuscript submitted). Thus, anti-Nef antibodies or synthetic inhibitors of Nef binding[147] may be considered for therapeutic purposes in HAND patients. Another approach is to target Nef. Several small molecule compounds targeting Nef have been described, but most of them were designed to neutralize the best-studied pathogenic activities of Nef—downregulation of CD4 and MHC 1.[48] These activities involve Nef domains that are different from the domains responsible for ABCA1 downregulation,[148] and the ability of those compounds to inhibit Nef-mediated impairment of cholesterol homeostasis has not been tested. Small molecule compounds that block Nef-mediated inhibition of cholesterol efflux have been described[148,149] and await validation in a HAND model.

7.4 | Epigenetic therapy and treatment of HAND

If a hypothesis that TRIM contributes significantly to the pathogenesis of HAND is confirmed, it follows that epigenetic therapies might be useful for the treatment of HAND. At the moment, epigenetic therapy is thriving with scores of drugs targeting epigenetic modifications being approved by the FDA,[150] mainly for cancer treatment.[151] These approaches were successfully applied for the treatment of several neurological disorders, including depression, addiction, and epilepsy.[152] While epigenetic modifications were shown to contribute to the pathogenesis of a number of neurodegenerative diseases,[153] we are not aware of epigenetic therapy to be used to treat them. Future studies will show if these approaches may provide special benefits in treating HAND.

8 | LIMITATIONS

In this article, we provide arguments for the central role of the Nef-cholesterol-lipid rafts axis in the pathogenesis of HAND. It should be noted that the proposed hypothesis is particularly relevant to ART-treated HIV infection when contribution of inflammation and immunodeficiency caused by replicating HIV is drastically reduced. This hypothesis is subject to several limitations. First, it assumes that similarities of clinical and pathological manifestations of HAND and other neurocognitive disorders, when they are documented, reflect similarities of their molecular and cellular mechanisms. Yet, as we note in this article, there are important differences in these manifestations[72,110,111] leaving door open for the possibility that pathogenesis of HAND is fundamentally different from other neurocognitive disorders and is based on as yet unknown mechanisms. However, we believe that the explanations for these differences can be provided within the proposed hypothesis, and there is no need to look for new ideas. Further, as mentioned above, PLWH are disproportionally affected by many physiological and psychosocial factors,[154] which may not be caused by Nef and can modify known pathogenic pathways and mechanisms, resulting in a very complex and variable presentation of this disease.

Second, cargo of Nef-containing EVs includes a multitude of other proteins and RNAs, both viral and originating from host cells. Quantitative abundance and even the presence of these factors may be affected by Nef expressed in the HIV-infected host cells, and these non-Nef factors may be responsible for the pathogenic properties of the Nef EVs. Similarities of the effects of recombinant Nef and Nef EVs, as well as inactivity of HIVΔNef,[41] make this possibility less likely, but do not allow us to completely rule out the contribution of indirect effects of Nef. However, regardless of whether the Nef effect is direct or is mediated by Nef-dependent changes in the cargo of EVs produced by HIV-infected cells, the proposed role of the Nef-cholesterol-lipid raft axis remains valid.

It is interesting to note that Nef is unique for HIV, while neurocognitive co-morbidities are characteristic for many other viral infections,[155] including COVID-19.[156] Mechanisms of neurocognitive impairments in other viral infections are likely different from those discussed here for HIV, but they still may include the cholesterol–lipid raft axis as a main component. The reason for this assumption is the influence of different viral infections on cellular cholesterol homeostasis,[157] thus potentially implicating the mechanisms described in this article.

9 | CONCLUSIONS

In this article, we presented arguments for the key role that impairment of cholesterol homeostasis by Nef EVs may play in the pathogenesis of HAND. Many of these arguments are hypothetical and remain to be tested experimentally. Nevertheless, they are consistent with findings in other brain diseases involving cognitive impairment. The proposed hypothesis is not intended to explain all features of HAND, but rather to outline a mechanism, which may have a considerable contribution to pathogenesis of a very complex disease. Most importantly, the proposed pathogenetic mechanisms suggest therapeutic approaches that have not yet been tested for HAND and may be effective in preventing or reversing this impairment.

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DATA AVAILABILITY STATEMENT

No new data. Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Abbreviations:

ABCA1	ATP binding cassette subfamily A member 1
Ac-CoA	Acetyl-coenzyme A
AD	Alzheimer's disease

AIBP	apolipoprotein A-I binding protein
AIDS	acquired immunodeficiency syndrome
ANI	asymptomatic neurocognitive impairment
APOE4	apolipoprotein E4
APP	amyloid precursor protein
ART	antiretroviral therapy
ASO	antisense oligonucleotide
BBB	blood brain barrier
CD4	clusters of differentiation 4
Cdc42	cell division control protein 42
COVID-19	Coronavirus Disease 2019
CSF	cerebro-spinal fluid
Env	envelope protein
EV	extracxellular vesicle
FDA	Food and Drug Administration
GTPase	guanosine triphosphate hydrolases
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorders
HIV	human immunodeficiency virus
IGF1R	Insulin-like growth factor-1 receptor
IL-6	Interleukin 6
KDM5	Lysine-specific demethylase 5
LXR	Liver X receptor
MHC	major histocompatibility complex
miRNA	micro RNA
MND	minor neurocognitive disorder
Nef	negative factor
NLRP3	nucleotide binding domain, leucine-rich–containing family, pyrin domain–containing-3

NMDA	N-methyl-D-aspartate
NNRTI	nonnucleoside reverse transcriptase inhibitor
NNTC	National NeuroAIDS Tissue Consortium
NRTI	nucleoside reverse transcriptase inhibitor
PCSK9	proprotein convertase subtilisin/kexin type 9
PLWH	people living with HIV
RNA	ribonuclear acid
SERINC5	serine incorporator 5
SIV	simian immunodeficiency virus
Tat	transactivator protein
TLR	toll-like receptor
TNFR	tumor necrosis factor receptor
TRIM	trained innate immunity

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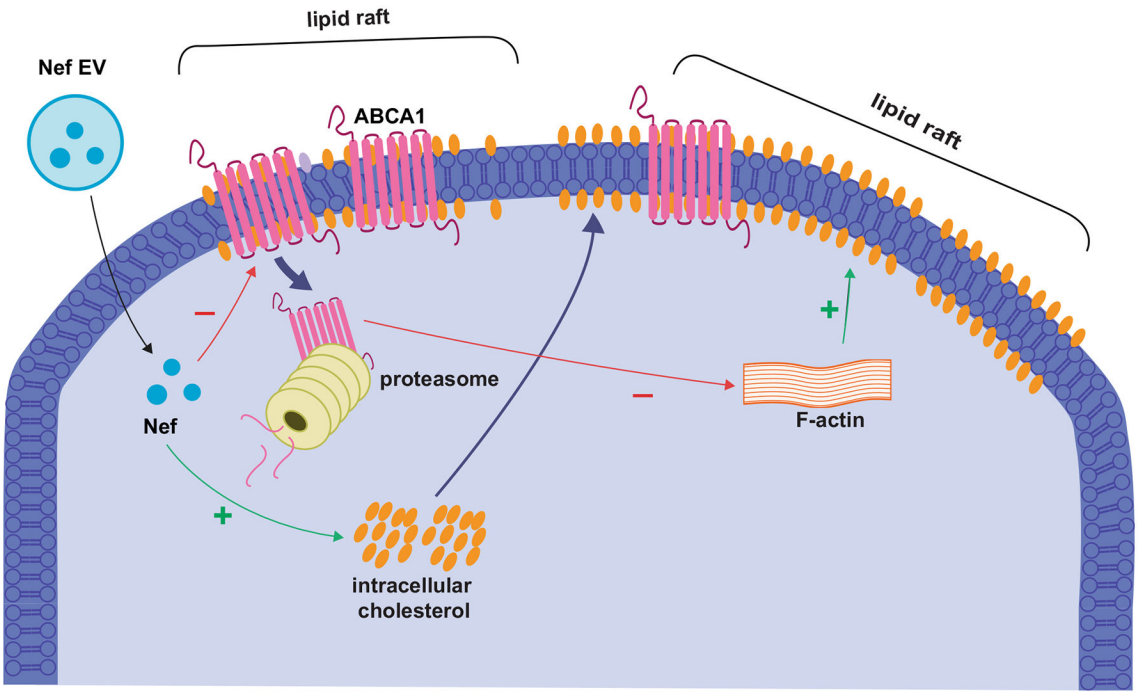

FIGURE 1.

A schematic diagram of the postulated effects of Nef EVs on cholesterol homeostasis in brain cells. Nef EVs deliver Nef to brain cells, where it affects cholesterol homeostasis by several mechanisms. Nef induces degradation of ABCA1 by the proteasomes; deficiency of ABCA1 results in diminished capacity for cholesterol efflux. Deficiency of ABCA1 also reduces β-actin polymerization, another mechanism leading to increased abundance of the lipid rafts. Nef also stimulates cholesterol biosynthesis, which contributes to the overloading of cells with cholesterol. The overall outcome is accumulation of intracellular cholesterol and modification and expansion of the lipid rafts. Colored arrows show the effects (green arrows with + sign show the stimulating effect, red arrows with − sign show the inhibiting effect), black arrows show the movement of the molecules.

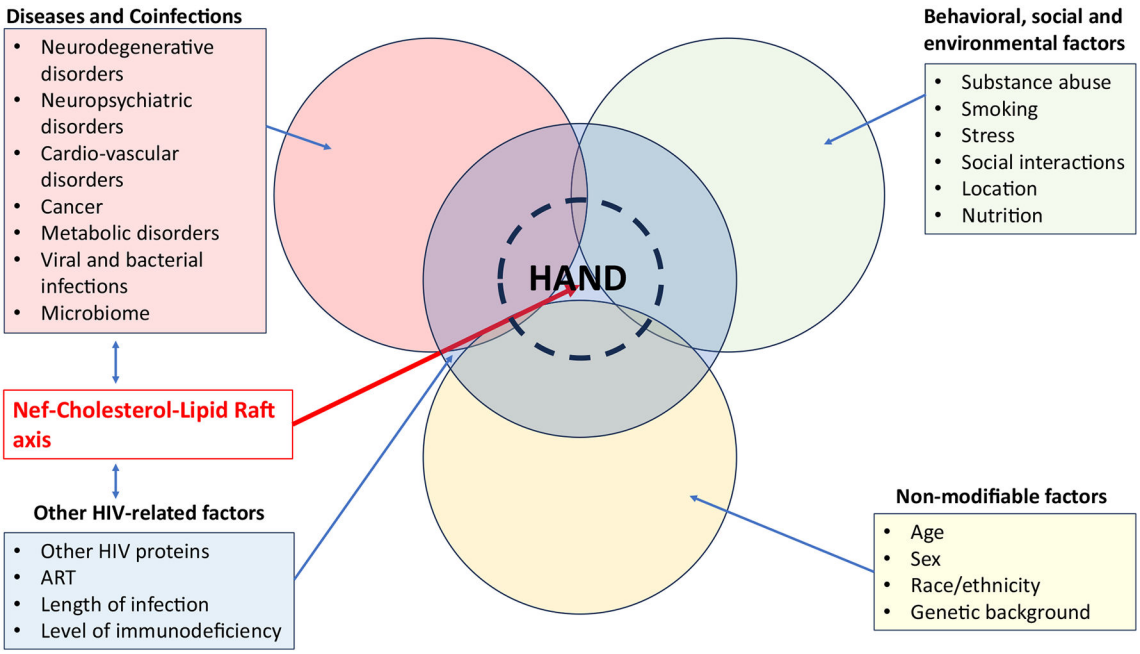

FIGURE 2.

Complexity of pathogenesis of HAND. HIV infection (blue circle) by definition is the key contributor to the pathogenesis of HAND with many other contributing factors greatly influencing the progression of the disease. These factors are grouped according to their common features; HAND is at the intersection of these groups (dash-line circle). The Nef-cholesterol-lipid raft axis is marked in red as it is proposed to be the main causative factor and underlies activity of some other contributing factors.

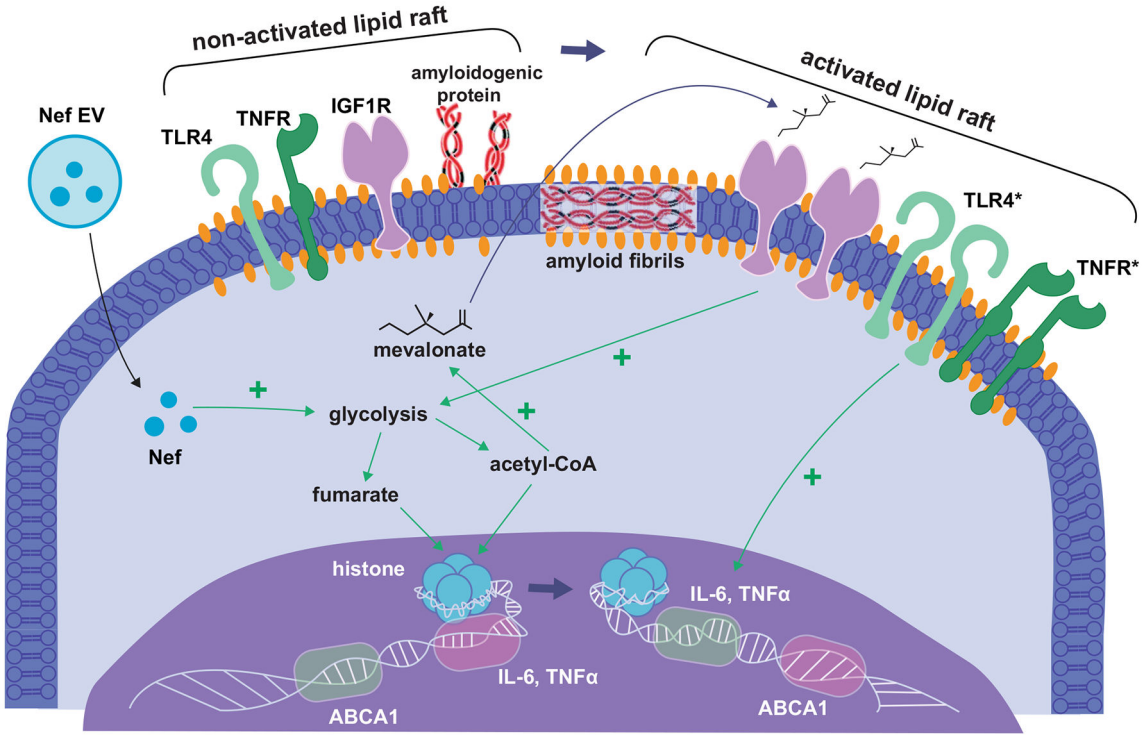

FIGURE 3.

A schematic diagram of the postulated changes in brain cells (neurons and glia) induced by Nef EVs. Modification and expansion of the lipid rafts caused by Nef lead to accumulation of amyloidogenic proteins in modified (activated) lipid rafts, their misfolding and aggregation, as well as enhanced presentation and activation (e.g., dimerization) of inflammatory (e.g., TLR4) and apoptotic (e.g., TNFR) receptors and inflammatory responses. In parallel, Nef induces glycolysis that stimulates production of fumarate and acetyl-coenzyme A, which induces epigenetic changes (green boxes mark active chromatin and red boxes mark inactive chromatin) that promote the expression of the proinflammatory cytokines by glia and suppress the expression of ABCA1. Acetyl-coenzyme A also stimulates the synthesis of mevalonate, which is secreted outside and stimulates the IGF1R initiating signaling that further activates glycolysis. Green arrows (with or without the + sign) mark a stimulating effect, black arrows show the movement of the molecules or conversion of the cell structure.